IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Shirai, et al.
App. No	:	10/521,958
Filed	:	January 21, 2005
For	:	INDOMETHACIN EXTERNAL PREPARATION
Examiner	:	Jean-Louis, Samira JM
Art Unit	:	4173
Conf #	:	2101

DECLARATION UNDER 37 CFR 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

We, Makoto Kanebako and Hitomi Chiba , declare as follows

1. We are researchers in Kowa Company Fuji Research Laboratory.

2. We are familiar with US Application No. 10/521,958, including the claims and the office action sent October 18, 2007.

3. We understand that the claims have been rejected over JP Publication No. 10-182458 (Kimura).

4. In order to establish that only specific surfactants such as glyceryl monostearate, sorbitan monostearate, stearyl alcohol, and polyethylene glycol monostearate having a melting point of 40°C or higher are effective in the claimed composition, the following experiments have been performed.

5. Using the methods described in the specification of US Application No. 10/521,958, the components shown in Tables 1 and 2 were used to produce formulations 1 to 15 (see Tables 1 and 2). Formulations 2-7 show that when the oil component is 3% by weight, as in Kimura, there is no separation of the oil layer and the aqueous layer. Formulations with a low oil content do not have a phase separation problem.

6. Table 2 shows formulations 8-15 which are analogous to the formulations of Table 1, except that they have higher (7%) oil composition. In formulations 8, and 11-15, phase separation was observed after storage for 1 or 2 months at 5°C. The higher weight percent oil results in an unstable formulation in which phase separation occurs upon storage. In contrast, formulations 9 and 10 each include a surfactant according to the invention and are stable, even with the higher oil content.

7. Table 3 provides melting point information for the surfactants used in Formulations 2-15. Formulations 9 and 10, in which 7% oil was used in combination with a surfactant according to the claimed invention (glyceryl monostearate or polyethylene glycol monostearate (40EO) having a melting temperature of 40°C or higher), were stable for at least 2 months at 5°C, even though the oil concentration was high.

8. We conclude that inclusion of a surfactant which is glyceryl monostearate, sorbitan monostearate, stearyl alcohol, or polyethylene glycol monostearate having a melting point of 40°C or higher, is critical when a higher oil content is used.

9. The advantages of high oil content are shown in Table 4. The gel-cream formulations of the invention do not exhibit any sticky feeling or irregularities after the use thereof. However, the gel formulations similar to Kimura exhibit a sticky feeling and irregularities. The absorbability of indomethacin through the skin is excellent as compared to Kimura.

10. We declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these

statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States codes and that such willful, false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: January 9, 2008 By: Makoto Kandatsu

Dated: January 8, 2008 By: Hitomi Chiba

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Table 1 (**3 wt%** of oil component)

Component		Formulation (wt%)						
		1	2	3	4	5	6	7
Indomethacin		1.0	←	←	←	←	←	←
Octyldodecyl Myristate		1.5	←	←	←	←	←	←
Diisopropyl Adipate		1.5	←	←	←	←	←	←
Carboxyvinyl Polymer		1.5	←	←	←	←	←	←
Hydroxypropyl-Methylcellulose 2910		0.5	←	←	←	←	←	←
L-menthol		3.0	←	←	←	←	←	←
Polyethylene glycol 400		1.0	←	←	←	←	←	←
Isopropanol		36.0	←	←	←	←	←	←
EDTA 2Na		0.01	←	←	←	←	←	←
sodium bisulfite		0.04	←	←	←	←	←	←
Diisopropanolamine		0.8	←	←	←	←	←	←
Water		53.15	51.15	←	←	←	←	←
Glyceryl monostearate (MGS)		-	2.0	-	-	-	-	-
Polyethylene glycol monostearate (40EO)		-	-	2.0	-	-	-	-
Polyoxyethylene (5) hydrogenated castor oil		-	-	-	2.0	-	-	-
Polyoxyethylene (50) hydrogenated castor oil		-	-	-	-	2.0	-	-
Polyoxyethylene (2) oleyl ether		-	-	-	-	-	2.0	-
Polyoxyethylene (5) behenyl ether		-	-	-	-	-	-	2.0
Total		100	←	←	←	←	←	←
Phase Separation stability	Initial	○	○	○	○	○	○	○
	Stored for 1 month (5°C)	○	○	○	○	○	○	○
	Stored for 2 month (5°C)	○	○	○	○	○	○	○
Criteria for evaluation		<○; Phase separation was not observed> <×; Phase separation was observed>						

Table 2 (**7 wt%** of oil component)

Component		Formulation (wt%)							
		8	9	10	11	12	13	14	15
Indomethacin		1.0	←	←	←	←	←	←	←
Octyldodecyl Myristate		3.5	←	←	←	←	←	←	←
Diisopropyl Adipate		3.5	←	←	←	←	←	←	←
Carboxyvinyl Polymer		1.5	←	←	←	←	←	←	←
Hydroxypropyl-Methylcellulose 2910		0.5	←	←	←	←	←	←	←
L-menthol		3.0	←	←	←	←	←	←	←
Polyethylene glycol 400		1.0	←	←	←	←	←	←	←
Isopropanol		36.0	←	←	←	←	←	←	←
EDTA 2Na		0.01	←	←	←	←	←	←	←
sodium bisulfite		0.04	←	←	←	←	←	←	←
Diisopropanolamine		0.8	←	←	←	←	←	←	←
Water		49.15	47.15	←	←	←	←	←	←
Glyceryl monostearate (MGS)		-	2.0	-	-	-	-	-	-
Polyethylene glycol monostearate (40EO)		-	-	2.0	-	-	-	-	-
Polyethylene glycol monostearate (4EO)		-	-	-	-	-	-	-	2.0
Polyoxyethylene (5) hydrogenated castor oil		-	-	-	2.0	-	-	-	-
Polyoxyethylene (50) hydrogenated castor oil		-	-	-	-	2.0	-	-	-
Polyoxyethylene (2) oleyl ether		-	-	-	-	-	2.0	-	-
Polyoxyethylene (5) behenyl ether		-	-	-	-	-	-	2.0	-
Total		100	←	←	←	←	←	←	←
Phase Separation stability	Initial	○	○	○	○	○	○	○	○
	Stored for 1 month (5°C)	×	○	○	×	×	×	×	×
	Stored for 2 month (5°C)	×	○	○	×	×	×	×	×
Criteria for evaluation		<○; Phase separation was not observed> <×; Phase separation was observed>							

Table 3 <List of melting point of surfactants used in Additional Example 1 >

Surfactants	Brand name (manufacturer)	Melting point (°C)	Formulation NO.
Glyceryl monostearate (MGS)	NIKKOL MGS-F20 (Nikko Chemicals Co., Ltd.)	54-58	2 and 9
Polyethylene glycol monostearate (40EO)	NIKKOL MYS-40 (Nikko Chemicals Co., Ltd.)	42-47	3 and 10
Polyethylene glycol monostearate (4EO)	NIKKOL MYS-4 (Nikko Chemicals Co., Ltd.)	31-36	15
Polyoxyethylene (5) hydrogenated castor oil	HCO-5 (Nikko Chemicals Co., Ltd.)	*	4 and 11
Polyoxyethylene (50) hydrogenated castor oil	HCO-50 (Nikko Chemicals Co., Ltd.)	22-27	5 and 12
Polyoxyethylene (2) oleyl ether	NIKKOL BO-2 (Nikko Chemicals Co., Ltd.)	*	6 and 13
Polyoxyethylene (5) behenyl ether	NIKKOL BB-5 (Nikko Chemicals Co., Ltd.)	55	7 and 14

*; Liquid at normal temperature (15-25°C)

Table 4

Component		Example 1 (present invention) (wt%)	Example 3 (Kimura) (wt%)
Indomethacin		1	1
Chlorpheniramine maleate		-	0.01
Octyldodecyl Myristate		5	-
Diisopropyl Adipate		5	3
Carboxyvinyl Polymer		1.5	1.5
Hydroxypropyl-Methylcellulose 2910		0.5	-
Polyvinyl pyrrolidone		-	0.5
L-menthol		3	-
Polyethylene glycol 400		1	-
1,3-Butylene glycol		-	8
Isopropanol		36	-
Modified ethanol		-	30
EDTA 2Na		0.01	-
sodium bisulfite		0.04	-
Diisopropanolamine		0.8	1.83
Water		44.15	49.16
Glyceryl monostearate (MGS)		2	-
Polyethylene glycol monostearate		-	5
Total		100	100
Aspect	Appearance	white turbidity (emulsifying)	transparence
	Fomulation	gel-cream	gel
Use feeling	Sticky feeling	o	×
	Occurrence of irregularities	o	×
Concentration of indomethacin in the skin (Ratio to the result of Example 1)		1	0.6